REMARKS

Applicants express appreciation to the Examiner for entering Applicants' submission filed February 24, 2004.

Reconsideration and withdrawal of the rejections of record in view of the foregoing amendment and the following remarks is respectfully requested.

Brief Summary of Telephone Call to Examiner

Applicants express appreciation for the courtesies extended by the Examiner to Applicants' representative, Charles Niebylski during a January 19, 2005 telephone call. During the telephone call, the Notice to Comply with Requirements for Patent Applications Containing Nucleotide and/or Amino Acid Sequence Disclosures was discussed. The Examiner indicated that each of the sequences in claims 7-9 require separate SEQ ID NOs, and Applicants should add the sequences to a substitute Sequence Listing, and add sequence identifiers throughout the specification and claims.

The Examiner also indicated during a telephone call on January 24, 2005, with Applicant's representatives, Charles Niebylski and Tu Phan, that all sequences in the claims and specification should be amended to include SEQ ID NOs to be in compliance with M.P.E.P. §714(R)(2). In particular, the Examiner indicated that withdrawn claims with sequences should also be amended to include the SEQ ID NOs and designated as "withdrawn and currently amended."

Response to Restriction Requirement

Applicants note that the Examiner has maintained the restriction requirement, and claims 3, 4, 10, 11, 18-32, 34-35, 43-46, and 48-50 remain withdrawn from consideration. However, Applicants request that claims 3, 4, 10, 11, 18-32, 34-35, 43-46, and 48-50 be permitted to remain pending subject to rejoinder should any of the pending claims be found to be allowable or upon allowance of the pending claims.

Applicants respectfully submit that the restriction requirement is in error and should be withdrawn. Specifically, Applicants note that there is a significant amount of overlap in the Groups set forth by the Examiner. There should be no undue burden for the Examiner to examine each of the groups of invention. Therefore, the restriction should be withdrawn.

Furthermore, Applicants remind the Examiner that if a generic claim is found to be allowable, the claims of the nonelected species should be examined if they depend from or otherwise include each of the limitations of the allowed generic claim. See M.P.E.P. § 809.02(c). Therefore, in the present case, if generic claim 1 is found to be allowable, Applicants submit that, at least claims 3-4, 18, 25-26, 29-33, 46 and 48-50, plus any other claim the Examiner deems proper, should be considered, rejoined and allowed.

Response to Notice to Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures

The rejection asserts that sequence disclosures in Applicants' application fail to comply with 37 C.F.R. 1.821(d), and that the specification and claims disclose nucleotide and amino acid sequences that are not identified by sequence identifiers as required for applications containing nucleotide/amino acid sequences. The rejection asserts that in order to comply with sequence rules, it is necessary to include the sequence in a Sequence Listing and identifying the sequences with "SEQ ID NO."

In response, Applicants request replacement of the Sequence Listing filed May 8, 2002, with the substitute Sequence Listing filed herewith along with a Statement that the Content of the Paper and Computer Readable Copies are the Same. Applicants note that SEQ ID NOs: 18-22 have been added to include the sequences disclosed in the original specification at pages 7-10, 15, 24-26, 29, and 30, and in claims 7-9. No new matter has been added.

Summary of Status of Amendments and Office Action

In the present amendment, claims 2, 5-9, 13, 16-17, and 33 are amended and claims 3, 4, 10, 11, 18-32, 34-35, 43-46, and 48-50 remain withdrawn from consideration. Therefore, claims 1-2, 5-9, 13, 16-46, and 48-51 are pending with claims 1, 5-6, 36, and 51 being independent.

Claims 1-2, 5-9, 13, 16-17, 33, 36-42 and 51 are under consideration.

In the present amendment, claim 2 is amended to recite " the gene mutated mouse according to claim 1." Claims 5 and 6 are amended to recite "mouse presenilin-1 protein as set forth in SEQ ID NO: 3." Claims 7-9 are amended to include sequence identifiers. Claim 13 is amended to remove "non human." Claim 16 is amended to recite "wherein the mutant presenilin-1 gene is transferred by homologous recombination." Claim 17 is amended to recite "wherein amount of the amyloid protein expression in a brain tissue of said gene-mutated mouse." Applicants note that support for these amendments are found throughout the specification. Furthermore, the specification at pages 7-10, 15-16, 24-26, and 29-30 are amended to include SEQ ID NOs for the sequences disclosed therein. Applicants reserve the right to pursue canceled subject matter in a divisional or continuation application. No new matter has been added.

Applicants also note that withdrawn claims 19, 20, 24, and 9 are amended in compliance with M.P.E.P. §714(R)(2).

Claims 1, 2, 5-9, 13, 16-17, 33, 36-42, and 51 are rejected under 35 U.S.C. §112, first paragraph as containing subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 1, 2, 5-9, 12-17, 33, 36-42, and 51 are rejected under 35 U.S.C. §112, first paragraph as not enabled.

Claims 2, 5, 7-9, 13, 16, and 17 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 2 is rejected because the recitation "the gene mutated animal according to claim 1" lacks antecedent basis because claim 1 allegedly does not recite such a limitation. Claim 5 is rejected because the recitation "presenilin-1 protein" is allegedly not clear as to which presenilin-1 protein is claimed.

Disclosure Statement

Applicants request that the Examiner include an initialed copy of the Form PTO-1449, accompanying the Supplemental Information Disclosure Statement filed May 29, 2003, with the next communication from the U.S. Patent and Trademark Office.

Response to §112 Rejections

Rejections for Written Description

Claims 1, 2, 5-9, 13, 16-17, 33, 36-42 and 51 are rejected under 35 U.S.C. §112, first paragraph as containing subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, as set forth in the previous office action of November 8, 2002, and July 30, 2003.

Initially, Applicants note that the Examiner in the Office Action of November 8, 2002, asserted that "[t]he specification provides examples of making a knockout transgenic mouse whose Presenilin-1 gene has a mutation of isoleucine at 213 has been mutated. The specification also teaches plasmid to make the transgenic mouse." Furthermore, during a telephone interview with Applicants' representatives on December 23, 2003, the Examiner noted that amending the claim to gene-mutated mouse would help to overcome the written description rejection. In response and without expressing agreement or acquiescence with the rejection, Applicants amended the claims to recite a "knockin gene-mutated mouse" in the Amendment filed on December 30, 2003. Therefore, Applicants respectfully note that the present rejection is misplaced because the rejection has already been addressed by Applicants in a previous Amendment, and communication with the Examiner. However, in order to expedite prosecution of the present amendment, Applicants note that the claims explicitly state that the gene-mutated animal is a mouse.

Further, as the specification sets forth on pages 11-23, knockin gene-mutated mouse is created using embryonic stem (ES) cells, and the cells are transformed using a vector which replaces the naturally occurring presenilin-1 gene with that encoded in the vector by homologous recombination. The identity of the mutations is known prior to insertion into the chromosome, and the transformed ES cells are "sprinkled" onto 8-cell mouse embryos and reinserted into pseudo-pregnant mice to produce chimeric offspring having the mutant presenilin-1 gene. These chimeric mice are then mated

with other mice to ultimately produce homozygous mutant presenilin-1 mice. Therefore, the specification provides a description of the invention in such a way as to reasonably convey to one of ordinary skill in the art that the inventors, at the time the application was filed, had possession of the claimed knockin gene-mutated mouse.

Therefore, the rejection of claims 1, 2, 5-9, 13, 16-17, 33, 36-42, and 51 under 35 U.S.C. § 112, first paragraph should be withdrawn.

Rejections for Enablement

Claims 1, 2, 5-9, 12-17, 33, 36-42, and 51 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Examiner asserts that the claims contain subject matter that is not described in the specification in such a way as to enable one of skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons set forth in the previous Office Actions dated November 8, 2002, and July 30, 2003.

In response, Applicants note that the Examiner in the Office Action dated November 8, 2002, acknowledged that the specification was "enabling for a knockout transgenic mouse whose endogenous preenilin-1 gene has been mutated by homologous recombination, a cell isolated from the transgenic mouse and a method of using the transgenic mouse for evaluating therapeutic compound that is useful in treating or preventing Alzheimer's disease." Applicants note that the claims have been amended, without acquiescence, to recite "gene-mutated mouse."

Furthermore, one of ordinary skill in the art would know that the specification enables Applicants' claimed invention. Applicants note that among other places in the specification, pages 11-23, Figs. 1-2, and 8, and the Examples provide sufficient disclosure to enable the claimed invention. In particular, Fig. 1 shows a restriction map of a chromosomal DNA fragment Pα containing exon 8 of mouse presenilin-1 which was cloned from a mouse genomic DNA library, Fig. 2 is a schematic plasmid pmX-1 containing a partial region of exon 8 of the mouse presenilin-1 gene with an OS-2 type mutation introduced by site-directed mutation, and Fig. 8 shows the results of electrophoresis on a 1% agarose gel of the PCR product obtained from chromosomal DNA cut from the tail of a progeny that resulted from mating a male mouse having an OS-2 mutant presenilin-1 gene with an F4 of CAG-cre#13 female mouse. Furthermore, the production of a gene-mutated animal is disclosed in detail from the middle of page 16 to the end of the first full paragraph on page 23. For example, page 16, last paragraph discloses preparation of a probe for PCR by obtaining a DNA fragment comprising a site for mutation in exon 8 of a presenelin-1 gene from a mouse genomic DNA library. The first and second full paragraphs of page 22 disclose obtaining gene-mutated animals having both the gene encoding APP mutant and the mutant presenelin-1 gene, and confirmation of possession of the gene encoding the APP mutant and mutant presenelin-1 gene from the tails of progeny. Example 1 discloses the construction of a probe for isolating a chromosomal DNA containing exon 8 of the mouse presenilin-1 gene, and Example 2 discloses the construction of a plasmid pX-1

to introduce mutations. Additionally, page 23, first full paragraph discloses isolation of cells from the claimed gene-mutated animal for use as a primary cell culture and subculture, and lines 1-12 of page 23 discloses administering test substances to the claimed gene-mutated animal to evalulate substances useful for preventive and/or therapeutic treatment of Alzheimer's disease.

Therefore, it is within the scope of common technical knowledge of one of ordinary skill in the art, and one of ordinary skill in the art would understand, from the abundant guidance set forth in Applicants' specification, how to obtain the claimed knockin gene-mutated mouse, primary cell culture or a subcultured cell obtainable by isolating a cell from such gene-mutated mouse, and methods for evaluating the therapeutic effect or preventive treatment of a substance on Alzheimer's disease comprising administering a test substance to a gene-mutated mouse.

For these reasons, Applicants' claims are enabled, and the rejection of claims 1, 2, 5-9, 12-17, 33, 36-42, and 51 under 35 U.S.C. §112, first paragraph should be withdrawn.

Rejections for Indefiniteness

Claims 2, 5, 7-9, 13, 16, and 17 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In response, Applicants respectfully submit that the claims pending prior to the

present amendment definitely define what Applicants consider to be their invention. However, in order to advance prosecution of the present application, and without acquiescence, Applicants have made the following amendments.

Claim 2 is rejected because the recitation "the gene mutated animal according to claim 1" lacks antecedent basis because claim 1 does not recite such a limitation.

In response, claim 2 has been amended to recite a gene mutated mouse according to claim 1."

Claim 5 is rejected because the recitation "presenilin-1 protein" is not clear as to which presenilin-1 protein is claimed.

In response, claim 5 has been amended to recite a mouse presenilin-1 protein.

Claims 7-9 are rejected because the recitation "a DNA sequence encoding around an amino acid at position 213....mutated" is unclear for being vague and indefinite.

In response, Applicants submit that one of skill in the art would understand from reading the specification, especially pages 6-7, 9 (last paragraph), and 15, that "a DNA sequence encoding around an amino acid at position 213....mutated" means that one or more amino acids at selected positions is substituted with different amino acid(s) in an amino acid sequence of presenilin-1 protein (page 6, second full paragraph). Examples of what is meant by mutating a DNA nucleotide sequence encoding amino acids around position 213 of the amino acid sequence of the presenilin-1 protein is disclosed on page 9 (last paragraph), page 15 (lines 7-28), and Example 3.

Claim 13 is rejected because the metes and bounds of the recitation "induces the production of amyloid β protein in an amount sufficient to form a progressive neural disease in a peripheral portion of the cerebral cortex" is unclear.

In response, Applicants note that pages 8, 14, and 21 of the specification provides sufficient disclosure such that one of ordinary skill in the art would understand from reading the specification, that mutant presenilin-1 protein induces the amyloid β protein production in an amount for a sufficient recognition of a substantial difference in the evaluation of degrees of memory disorder, pathological observations, and various neural disorders as compared to a normal animal.

Claim 16 is rejected because the recitation "wherein the presenilin-1 gene is transferred by homologous recombination" lacks antecedent basis since claim 1 dos not recite transfer of presenilin-1 gene.

In response, Applicants have amended the claim to recite "wherein the mutant presenilin-1 gene is transferred by homologous recombination."

Claim 17 is rejected because the recitations "a brain" and "sufficient to cause affected behavior in a memory learning test" are unclear.

In response, Applicants have amended claim 17 to recite "a mouse brain." Furthermore, Applicants note that it would be clear to one of skill in the art from reading the specification, especially page 14 (second paragraph), that the recitation "sufficient to cause affected behavior in a memory learning test" means the amount of amyloid β protein is increased to an amount that is sufficient to recognize substantial differences

in the evaluation of degrees of memory disorder, pathological observations, and various neural disorders in comparison to a normal animal.

For these reasons, Applicants respectfully request that the Examiner withdraw the rejection of claims 2, 5, 7-9, 13, 16, and 17 under 35 U.S.C. §112, second paragraph.

CONCLUSION

For the reasons advanced above, Applicants respectfully submit that all pending claims patentably define Applicants' invention. Allowance of the application with an early mailing date of the Notices of Allowance and Allowability is therefore respectfully requested.

Respectfully Submitted,
Masatoshi TAKEDA et al.

Bruce H. Bernstein
Reg. No. 29,027

Stephen M. Roylance
Reg. No. 31,296

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GREENBLUM & BERNSTEIN, P.L.C.
1950 Roland Clarke Place
Reston, VA 20191
(703) 716-1191